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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/170,980	10/13/1998	JENNIFER L. HILLMAN	PF-0195-1DIV	7498

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LEGAL DEPARTMENT
INCYTE GENOMICS, INC.
3160 PORTER DRIVE
PALO ALTO, CA 94304

EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	17

DATE MAILED: 11/26/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/170,980	Hillman et al
Examiner	**Art Unit**
MINH TAM DAVIS	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 16, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 11-16, and 18-26* is/are pending in the application.

4a) Of the above, claim(s) *11-16 and 21-24* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 18-20, 25, and 26* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant adds new claims 25, 26, which are related to claims 1, 18-20 and are not new matter.

Accordingly, claims 1, 18-20, 25-26 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 101, UTILITY

Claims 1, 18-20 remain rejected under 35 USC 101 for the reasons previously set forth in Paper No. 13, pages 1-6. New claims 25-26 are rejected for the same reasons previously set forth in Paper No. 13.

Applicant argues that the claims have patentable utility and a well known utility based on 1) the strong chemical and structural homology of the claimed HPAK protein (SEQ ID NO:1) with known human pancreatic kallikrein (54% sequence identity), and 2) the presence of four non-contiguous conserved amino acid residues for serine protease, which is likely to confer chymotrypsinogen-like activity, and 10 conserved cysteine, which are structurally important and

involved in the formation of 5 disulfide bonds. Thus the claimed HPAK protein has numerous practical, beneficial uses in toxicology testing, drug development and the diagnosis of diseases characterized by expression of HPAK, none of which necessarily require detailed knowledge of how the polypeptide coded for by the polynucleotide works.

Applicant summarizes case law on the utility requirement at pages 3-4 of Paper No. 14.

Applicant argues at pages 5-19 that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of diseases characterized by expression of HPAK, and that these uses are "well-established". It is noted that toxicology testing and drug discover are not specifically recited in the specification as originally filed.

It is further noted that SEQ ID NO:1 is a deduced amino acid sequence from a polynucleotide sequence of SEQ ID NO:2. It is not clear whether SEQ ID NO:1 exists in nature. Applicant has not answered to this issue. The specification discloses isolation of a polynucleotide sequence of SEQ ID NO:2 from a breast cDNA library (Examples I-V, pages 37-42). No disclosure of detection of SEQ ID NO:1 in any tissue is found in the specification. Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than

the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation or the extent of translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. For the above reasons, one of skill in the art would not be able to predict if SEQ ID NO:2 is translated into a polypeptide expression product

Applicant argues that toxicology testing is a well-established utility and concludes that the claimed polynucleotides could be used in this manner and that the claimed invention possesses utility. This is not persuasive because for a utility to be "well-established" it must be specific, substantial and credible. In this case, as indicated at page 6, paragraph before last, especially last three lines of the response of 04/16/01, all expressed genes are in some combination useful in toxicology testing. However, the particulars of toxicology testing with

HPAK protein (SEQ ID NO:1) are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to HPAK protein (SEQ ID NO:1). Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polynucleotide in an array for toxicology screening or expression profiling is only useful in the sense that the information that is gained from the array or profile is dependent on the pattern derived from the array or profile, and says nothing with regard to each individual member of the array or profile. Again, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicant's individual polynucleotide is affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polypeptide have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding the polypeptide could be put.

Applicant states that biochemical pathway elucidation, drug target identification and assessment of toxicity and treatment efficacy in drug development apply to virtually every

member of the general class of expressed polynucleotides and the encoded proteins thereof which are expressed in human, and cites the potential benefit to the public of the uses of screening assays. This is not persuasive because in the absence of any disclosed relationship between the claimed polypeptide and any disease or disorder and the lack of any correlation between the claimed polypeptide with any known disease or disorder, any information obtained from a screening assay would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPO at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

At page 8, Applicant argues that "the rejection is made based on a scientifically incorrect and legally unsupportable assertion that the identification of the family or families of proteins to which the claimed invention belongs, without more, does not satisfy the utility requirement". This is not persuasive because the rejection is based on the failure to disclose sufficient properties of the polynucleotides to support an inference of utility. HPAK protein (SEQ ID NO:1) has not been shown to belong to a family of kallikreins. The only showing is that the deduced protein of SEQ ID NO:1 encoded by the claimed polynucleotide of SEQ ID NO:2 has 54% sequence identity to a human pancreatic kallikrein. Although kallikrein has chymotrypsinogen-like activity (specification, page 1), neither the specification, nor the art of record teaches any association of HPAK protein with chymotrypsinogen-like activity. Moreover,

although the claimed SEQ ID NO:1 has four conserved amino acid residues for serine protease, and 10 cysteines, there is no indication that these four amino acids alone or 10 cysteine alone would confer serine protease activity. Further, there is no teaching of consensus sequences that would suggest that the claimed HPAK protein has chymotrypsinogen-like activity, and is part of the kallikrein family. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. However, this is not the case for the claimed invention as no function in common with the kallikrein family has been elucidated for the claimed HPAK.

At page 8, Applicant argues that a patent application can specify a utility without any knowledge as to how or why the invention has that utility. This is not persuasive because the utility must be specific, substantial and credible. Applicant's assertion that the claimed invention has utility in toxicology testing, drug development and disease diagnosis, as well as in the diagnosis, prevention and treatment of diseases associated with expression of HPAK protein do not meet the standards for a specific, substantial, and credible or well-established utility for reasons set forth above.

At pages 9, Applicant states"unlike the synthetic molecules of Kirk and Ziegler, the claimed invention is **known** to be useful, because it is expressed in human, for use in toxicology

testing, drug development and disease diagnosis. This is not persuasive because it is questionable whether the claimed HPAK protein is expressed in human, *supra*. Further, the specification does not disclose the significance of any test results, nor is there any evidence that the significance was known as of the filing date. If the expression of the claimed polypeptide increases, is this a positive or negative outcome? Would this be a toxic response or not? The disclosure is insufficient to evaluate the results of the test in any meaningful manner. Applicant further argues that the claimed polypeptide could serve "as a marker of a toxic response, or alternatively, if levels of the claimed polypeptide remain unchanged during a toxic response, as a control in toxicology testing". This is not persuasive because this use is speculative at best, as well as not being specific or substantial in that any polynucleotide may possess the property of being a marker or a control for some toxic response. It would appear that Applicant is describing a "wish to know" type of utility, which is not a specific, substantial and credible utility. Applicant asserts that knowledge of the specific functions of the encoded protein, i.e. the function or role of the protein in its natural state, is not required for use of the polynucleotide in diagnosis of disease. This is not persuasive because the validity of this argument requires some correlation to a disease. On this record, such a correlation is absent.

At pages 9-12, Applicant argues that a utility may be specified even if it applies to a broad class of inventions. This is not persuasive because the proposition is not sufficient to establish utility for each member of the class. Specific utility must be shown or be evident for each member of the class. None of the utilities identified by Applicant, i.e. toxicology testing,

drug discovery, disease diagnosis, treatment and prevention of diseases associated with HPAK protein expression, have been demonstrated to be specific to HPAK. One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of HPAK protein.

On the other hand, practical utility can be inferred if each and every member of the broad class possesses a common utility. However, the fact situation in the instant application is not analogous to Applicant's fishing pole example. Applicant's expansion of this concept to different "classes" of proteins with the assertion that each "class" possesses a specific, substantial and credible or well-established utility is not persuasive. Whether the cited classes of proteins (interleukins, G-protein coupled receptors) do or do not possess a specific, substantial and credible or well-established utility is not to be decided in the instant application because the instant claims are not directed to interleukins, G-protein coupled receptors. The claimed invention does not encode a member of a protein family or a protein that is part of a "class" of polypeptides with a specific function. Applicant states that all (emphasis omitted) naturally-occurring polynucleotide and polypeptide sequences which are expressed can be used in a real-world context as tools for toxicology testing. This is not persuasive, as previously disclosed, since any information obtained from a screening assay, such as toxicology testing, would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object

of use-testing." *Brenner*, 148 USPO at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

Applicant asserts, at page 12, that the use of the claimed invention as a tool for toxicology testing is a practical, real world use and is a "substantial" use. As used in toxicology testing, drug discovery and disease diagnosis the claimed invention has a beneficial use in research other than studying the claimed invention itself. This is not persuasive because the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner*, the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPO at 690. Here, there is no evidence that the claimed polynucleotide encoding SEQ ID NO:3 or the polypeptide encoded thereby has any utility.

Applicants assert that the use of the claimed invention for toxicology testing, drug discovery, and disease diagnosis are substantial utilities. This is not persuasive because the question at issue is whether or not the broad general assertion that the claimed polypeptides might be used for *some* diagnostic application, *some* drug discovery or *some* toxicology test (in the absence of a disclosure of *which* diagnostic application, *which* drug discovery or *which* toxicology test) would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria *See In re Kirk*, 153 USPO 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention

of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.')

Applicant asserts, at page 13, that there exists a market "for databases containing all expressed genes". This is not persuasive because this assertion fails to address the utility of the individually claimed polypeptide. The claims are to isolated chemical compositions, not to descriptive information included in a database.

Applicant argues, at pages 13-17, that the Examiner failed to demonstrate that one of ordinary skill in the art would reasonably doubt the utility of the claimed invention, based on the homology or similarity of HPAK protein to a human pancreatic kallikrein. This argument is not persuasive because such evidence and scientific reasoning was presented in the grounds of rejection in Paper No.13, pages 3-6.

Applicant recites the reference by Brenner et al, which teaches that 30% sequence identity over at least 150 residues is a reliable measure of sequence homology. Applicant further argues that the claimed polypeptide share 54% identity with human pancreatic kallikrein, or an ungapped identity at 72 out of 110 residues, exceedings the thresholds proposed by Brenner et al. Thus SEQ ID NO:1 is a true kallikrein homolog by these criteria. Since these criteria are based

on a dataset of homologous proteins, one would likewise expect SEQ ID NO:1 to possess the evolutionarily conserved tructural and functional characteristics of kallikrein. Hence, the "reasonable correlation" standard as set by case law has been met.

This is not found to be persuasive, because although Applicant discloses a 54% identity of the claimed polypeptide with human pancreatic kallikrein, or an ungapped identity at 72 out of 110 residues, the relevance of the apparently arbitrarily chosen regions of identity is unclear since there is no suggestion, either in the specification or the art of record that any of these regions have been implicated in any chymotrypsinogen-like activity, or are consensus sequence of kallikrein. Further, although the claimed polypeptide has four conserved amino acids of serine protease, and 10 cysteines, there is no indication that these four amino acids or cysteines would confer serine protease activity. It would appear, if meaningful at all, that the similarities in these regions may be involved with as yet undefined biochemical properties and functions. The unpredictability of utilizing predicted structural determinations to ascertain functional aspects of the protein is further demonstrated by Bork, of record who teaches the pitfalls associated with comparative sequence analysis for predicting protein function and specifically states that conclusions from comparison analysis are often stretched with regard to protein products.

Applicant asserts that the references by Bowie et al in part counter to the outstanding rejection and in part supportive of the asserted utilities for the following reasons: Bowie et al teach that evaluating sets of related sequences which are members of the same gene family, is an accepted method of identifying functionally important residues which have been conserved over

the course of evolution. Applicant suggests that the amino acid differences between the claimed HPAK protein and kallikreins are likely to occur at positions of minimal functional difference while residues that are conserved are likely those that are important for protein function because of natural selection.

Further Applicant argues at page 16 that Lazar et al and Burgess at al are not relevant because they are drawn to mutagenesis of particular amino acid residues with known importance to function and are not analogous to molecular evolution which is profoundly influenced by natural selection and are likely to represent substitutions that do not alter protein function.

This is argument is not persuasive because no particular function has been ascribed to any domain of HPAK protein, and it is unknown what function, if any, might be conserved for natural selection. Further, because the differences between HPAK protein (SEQ ID NO:1) and a human pancreatic kallikrein involve 54% amino acid differences, as previously disclosed, the effects of these differences upon protein function cannot be predicted since as taught by Bowie et al, the amino acid sequence determines the shape and function of a protein and it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Although it is possible that there is an evolutionary relationship between the proteins encoded by the claimed polynucleotides and the prior art proteins, based on the information in the art or record and in the specification, the functions of those domains are unknown and no particular chymotrypsinogen-like activity, nor the function of the claimed HPAK protein can be ascribed to it based on sequence identity to the prior art

proteins. Further, although the claimed polypeptide has four conserved amino acids of serine protease, there is no indication that these four amino acids alone would confer serine protease activity. Although it is clear that methods are available to identify proteins with identity between primary amino acid sequences, it is well known and clearly understood in the art, as taught by Bowie et al that prediction of protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex, and it is also well known in the art, as exemplified by Lazar et al and Burgess et al that even a single amino acid change can alter protein function. The unpredictability of utilizing predicted structural determinations to ascertain functional aspects of the protein is further demonstrated by Bork, of record who teaches the pitfalls associated with comparative sequence analysis for predicting protein function and specifically states that conclusions from comparison analysis are often stretched with regard to protein products and specifically cites that most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality.

In addition, the Lazar et al and Burgess et al references, although drawn to site directed mutagenesis studies, clearly demonstrate that even a single amino acid alteration can alter the function of a protein. It would be expected that with the disclosed differences in amino acid composition, at least some of the amino acids required for any common function would be altered. Although the proteins show some identity, no conserved region with any chymotrypsinogen activity has been identified. Further, although the claimed polypeptide has

four conserved amino acids of serine protease, there is no indication that these four amino acids alone would confer serine protease activity. As previously disclosed, with these percent dissimilarities between the polypeptide encoded by the claimed invention and the prior art proteins, the effects of these dissimilarities upon protein structure and function cannot be predicted.

Concerning Bork et al, Applicant asserts that Bork et al emphases "high-throughput technologies". Applicant asserts that human pancreatic kallikrein on the other hand was analyzed by both laboratory and computational sequence analysis, not the allegedly error-prone high-throughput technologies being denounced by Bork. Applicant asserts that the classification of human pancreatic kallikrein as a serine protease of the kallikrein family is credible scientific evidence, and has been substantiated by peer review.

This argument is not persuasive, because although the classification of human pancreatic kallikrein as a serine protease of the kallikrein family is credible scientific evidence, and has been substantiated by peer review, the claimed classification of HPAK as a member of kallikrein has not been a credible scientific evidence, and has not been substantiated by peer review. Further, Applicant has not shown that the computational prediction for the claimed invention is any more accurate than the prediction accuracy from several references well known in the art, recited in table 1, and reviewed by Bork et al (Bork et al, of record, table 1 on page 399).

In view of the information known in the art, it could not be predicted that a determination of a chymotrypsinogen-like functional identity could be made based on sequence data alone.

Further, given the differences between HPAK protein and the prior art proteins, and given the unpredictability known in the art as evidenced by Bowie et al, Lazar et al and Burgess et al, as well as the unpredictability of the art of comparative sequence analysis to discern protein function from structure as taught by Bork, sequence identity alone cannot give a reasonable correlation between the structure and function of HPAK protein and the disclosed prior art proteins.

Applicant argues, on pages 17-19, that practical real-world uses are not limited to uses that are unique or particular to an invention and that broad classes of inventions can satisfy the utility requirements so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. This is not persuasive because the requirement in any particular case is that practical utility can be inferred if each and every member of the broad class possesses a common utility. None of the utilities identified by Applicant, i.e. toxicology testing, drug discovery, disease diagnosis, treatment of cell proliferative disorders have been demonstrated to be specific to the polynucleotide encoding HPAK or to the polypeptide encoded thereby. One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of the polynucleotide encoding HPAK or the polypeptide encoded thereby. Applicant's arguments have not been found persuasive and the rejection is maintained.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Rejection under 35 USC 112, first paragraph of claims 1 and 20 pertaining to lack of a clear written description remains for reasons already of record in paper No. 13. New claims 25-26 are rejected for the same reasons previously set forth in Paper No. 13.

Applicant argues that the specification discloses SEQ ID NO:1 and naturally-occurring sequences of SEQ ID NO:1 that have at least 90% identity of SEQ ID NO:1. Given SEQ ID NO:1, one skilled in the art would recognize naturally-occurring sequences of SEQ ID NO:1 that have at least 90% identity of SEQ ID NO:1.

Applicant argues that 1) In constrast to the situation of *Lilly* and *Fiers*, the present application defines polypeptides in terms of chemical structure, rather than on funtional characteristics, 2) The claimed genus is of narrow scope. In accordance with Brenner al, naturally occurring molecules may exist which could be characterized as glutathione peroxidases, and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The present claims recite a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to SEQ ID NO:1, which has only 253 amino acid residues. This variation is far less than 30% identity over at least 150 residues to SEQ ID NO:1, and 3) The state of the art at the time the invention was made is further advanced than at the time of the *Lilly* and *Fiers* application, for example, PCR, highly effecient cloning and DNA sequencing technology, large databases of protein and nucleic acid sequences, all of which did not exist at the time of the *Lilly* and *Fiers* application.

Applicant's arguments set forth in paper No.14 have been considered but are not deemed to be persuasive for the following reasons:

Although Applicant describes the structure of SEQ ID No:1, Applicant does not define the claimed numerous variants in term of chemical structure, i.e. the chemical structure of the claimed variants are not disclosed in the specifcation. The claims 1, 20, 25-26 read on variants of SEQ ID No:1 , wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the nucleic acid or peptide, as well as insertions and deletions, provided that the resulted variation is up to 10% difference with SEQ ID NO:1. The specification does not disclose which amino acid subjected to conservative or non-conservative substitution, or deletion, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. Thus the scope of the claims includes numerous structural variants. No common structural attributes that identify the claimed variants are disclosed. In addition, no common functional attributes that identify the claimed variants are disclosed, because the function of SEQ ID NO:1 is not known (see the above Utility rejection). The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed variants, SEQ ID NO:1 alone is insufficient to describe said variants. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of variants.

Further, in the absence of a teaching of the chemical structure of the claimed numerous variants, even with the advance of technology at the time the invention was made, one of skill in the art still could not identify the numerous claimed variants, using any of the cited technology, such as PCR, highly effecient cloning and DNA sequencing technology, large databases of protein and nucleic acid sequences. Thus the recited case law *Lilly* and *Fiers* still applies well to the present application, despite the advance of technology at the time the invention was made.

Therefore, applicant was not in possession of the claimed allelic variants.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Rejection under 35 USC 112, first paragraph of claims 1, 18-20 pertaining to lack of enablement due to lack of a well established utility remains for reasons already of record in paper No.13. New claims 25-26 are rejected for the same reasons previously set forth in Paper No. 13.

Applicant assertst that to the extent that the rejection under 112, first paragraph is based on the improper allegation of lack of patentable utility under 101, it fails for the same reason.

Rejection remains for the same reasons set forth under 101 rejection.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph of claims 1, 20, pertaining to lack of enablement for allelic variants of SEQ ID NO:1, remains for reasons already of record in paper No.13. New claims 25-26 are rejected for the same reasons previously set forth in Paper No. 13.

Applicant argues that given the information provided by SEQ ID NO:1, one of skill in the art would be able to routinely obtain a naturally-occurring amino acid sequences having at least 90% sequence identity to SEQ ID NO:1 by screening a cDNA library or use appropriate PCR conditions for the relevant polynucleotides/polypeptides that already exist in nature. One of skill in the art need not make and test vast number of polypeptides that are based on the amino acid sequences of SEQ ID NO:1.

Applicant's arguments set forth in paper No.14 have been considered but are not deemed to be persuasive for the following reasons:

The claims 1, 20, 25-26 read on allelic variants of SEQ ID No:1 , wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the nucleic acid or peptide, as well as insertions and deletions, provided that the resulted variation is up to 10% difference with SEQ ID NO:1. The specification does not disclose which amino acid are subjected to conservative or non-conservative substitution, or deletion, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. Thus the scope of the claims includes numerous structural variants that would exist in nature. No common structural attributes that identify the claimed variants are disclosed. Thus one of skill in the art would have expected a vast number of unrelated sequences, with unknown function, would be obtained by hybridization or PCR techniques based on the amino acid sequences of SEQ ID NO:1.

REJECTION UNDER 35 USC 102, NEW REJECTION

1. Claims 1, 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Fukushima, D et al, Genbank Sequence Database (Accession No: A24696), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available on 1985.

Claims 1, 25 are drawn to a naturally-occuring amino acid sequence having at least 90% sequence indentity to SEQ ID NO:1, and an immunogenic fragment of SEQ ID NO:1.

Fukushima, D et al teach an amino acid sequence which is 100% similar to SEQ ID NO:1 from amino acid 1 to 43.

Although Fukushima, D et al do not teach that the amino acid sequence is immunogenic, it is an inherent property of any peptide, because any peptide could elicit an immune response in an animal when injected into said animal. Thus the amino acid sequence taught by Fukushima, D et al meet all the limitations of the claims.

REJECTION UNDER 35 USC 103, NEW REJECTION

Claims 1, 20, 26 are rejected under 35 U.S.C. 103(a) as being obvious over Fukushima, D et al, in view of Johnstone and Thorpe (Immunochemistry in Practice, 2nd Ed., 1987, Blackwell Scientific Publications, Oxford, pages 49-50).

Claims 1, 20, 26 are drawn to a naturally-occuring amino acid sequence having at least 90% sequence indentity to SEQ ID NO:1, and an immunogenic fragment of SEQ ID NO:1 in a suitable pharmaceutical carrier.

The teaching of Fukushima, D et al has been set forth. Fukushima, D et al do not teach an amino acid sequence in a suitable pharmaceutical carrier.

Johnstone and Thorpe teach that it was common practice in the art at the time of applicant's invention to formulate compositions of antibodies and PBS, which is considered to be an acceptable carrier for storage of antibodies.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include a carrier in the composition because Johnstone and Thorpe teach that it was common practice in the art at the time of applicant's invention to formulate compositions of antibodies and PBS, which is considered to be an acceptable carrier for storage of antibodies, or proteins. One of ordinary skill would have been motivated to do so in order to develop compositions suitable for storage. Finally, it has been held by the Court that a compound and a carrier are obvious, if it is obvious in the art to utilize a carrier with related compounds. See *In re Rosicky*, 125 USPQ 341 (CCPA 1960).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of thisplication or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

November 13, 2001